E1 cont'd

B. Schneider, N. Thanki, H. Weissig, J. D. Westbrook and C. Zardecki, The Protein Data Bank, Acta Cryst. (2002). D58, 899-907); and BIND (Bader, et al., Nucleic Acids Res 29(1):242-245. (2001)).

*Please replace the paragraph found on page 13, beginning at line 21 with the following paragraph.*

E2

Similarly, structural alignment of structurally related proteins can be done to generate sequence alignments. There are a wide variety of such structural alignment programs known. See for example VAST from the NCBI (Gibrat, et al., Curr Opin Struct Biol 6(3):377-385. (1996)); SSAP (Orengo and Taylor, Methods Enzymol 266(617-635 (1996)) SARF2 (Alexandrov, Protein Eng 9(9):727-732. (1996)) CE (Shindyalov and Bourne, Protein Eng 11(9):739-747. (1998)); (Orengo et al., Structure 5(8):1093-108 (1997); Dali (Holm et al., Nucleic Acid Res. 26(1):316-9 (1998), all of which are incorporated by reference). These structurally-generated sequence alignments can then be examined to determine the observed sequence variations.

*Please replace the paragraph found on page 13, beginning at line 29 with the following paragraph.*

E3

Primary libraries can be generated by predicting secondary structure from sequence, and then selecting sequences that are compatible with the predicted secondary structure. There are a number of secondary structure prediction methods, including, but not limited to, threading (Bryant and Altschul, Curr Opin Struct Biol 5(2):236-244. (1995)), Profile 3D (Bowie, et al., Methods Enzymol 266(598-616 (1996); MONSSTER (Skolnick, et al., J Mol Biol 265(2):217-241. (1997); Rosetta (Simons, et al., Proteins 37(S3):171-176 (1999); PSI-BLAST (Altschul and Koonin, Trends Biochem Sci 23(11):444-447. (1998)); Impala (Schaffer, et al., Bioinformatics 15(12):1000-1011. (1999)); HMMER (McClure, et al., Proc Int Conf Intell Syst Mol Biol 4(155-164 (1996)); Clustal W (Higgins D., Thompson J., Gibson T.Thompson J.D., Higgins D.G., Gibson T.J.(1994). CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting,position-specific gap penalties and weight matrix choice. Nucleic Acids Res. 22:4673-4680); BLAST (Altschul, et al., J Mol Biol 215(3):403-410. (1990)), helix-coil transition theory (Munoz and Serrano, Biopolymers 41:495, 1997), neural networks, local structure alignment and others (e.g., see in Selbig et al., Bioinformatics 15:1039, 1999).

*Please replace the paragraph found on page 2, lines 4-6 with the following paragraph.*

E4

In particular, U.S.S.N.s 60/061,097, 60/043,464, 60/054,678; PCT US98/07254; and USSN: 09/127,926, now US Patent No. 6,269,312, issued July 31, 2001, describe a method termed "Protein Design Automation", or PDA™, that utilizes a number of scoring functions to evaluate sequence stability.